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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Pierre Lebreton

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EXAMINER

BLAND, LAYLA D

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/552,309	Applicant(s) LEBRETON, PIERRE	
	Examiner LAYLA BLAND	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 June 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-32 is/are pending in the application.
- 4a) Of the above claim(s) 28-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/7/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election with traverse of Group I in the reply filed on May 4, 2008 is acknowledged. The traversal is on the ground(s) that Balazs does not disclose the molecular weight of the polymers used in the examples. As stated in the requirement for restriction mailed April 2, 2008 and acknowledged in Applicant's response dated May 4, 2008, the terms "low molecular weight" and "high molecular weight" are relative terms. Balazs teaches cross-linked gels made of HA with other polysaccharides; the skilled artisan would understand that HA, carboxymethyl cellulose, collagen, and heparin have different molecular weights. Because "higher" and "lower" are relative terms, differing molecular weights necessarily are higher or lower than each other.

The requirement is still deemed proper and is therefore made FINAL.

Claims 28-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 4, 2008.

This application is a national stage entry of International Application No. PCT/FR04/00870, filed April 8, 2004, which claims priority to French Application No. 0304444, filed on April 10, 2003. The copy of certified copy of the priority has been filed with the instant Application. It is noted that French Application No. 0304444 is in French; no translation of said French application into English has been provided.

Claim Objections

Claim 25 is objected to because of the following informalities: the claim recites the limitations "3.10⁵ Da" and "3.10⁶ Da," which possibly should be "3 X 10⁵ Da" and "3 X 10⁶ Da." Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "low-molecular weight" and "high-molecular weight" in claim 17 are relative terms which render the claim indefinite. The terms "low-molecular weight" and "high-molecular weight" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 17 (and dependent claims) recites the limitation "polysaccharides and derivatives thereof." Neither the claim nor the specification defines which derivations or modifications of polysaccharides are encompassed by the claim. Page 5 of the specification exemplifies some derivatives, but exemplification is not definition.

Claim 17 (and dependent claims) recites the limitation “an effective and non-excessive amount of at least one crosslinking agent.” The specification provides no guidance for the determination of which amounts are effective and non-excessive. Thus, the skilled artisan would not be apprised of the metes and bounds of the claim.

Claims 18, 21, 22, 23, 24, and 25 all ultimately depend from claim 17 and recite the limitation “said mixture.” Claim 17 does not recite a mixture. There is insufficient antecedent basis for this limitation in the claims.

Claim 19 depends from claim 17 and recites the limitation “said polymer.” Claim 17 recites a cross-linked polymer, a low-molecular weight polymer, and a high-molecular weight polymer. It is unclear which of these is the “said polymer” recited in claim 19. There is insufficient antecedent basis for this limitation in the claim.

Claims 18, 20, 21, 23, 26, and 27 include the limitations “advantageously” and “very advantageously,” which are narrower statements of the broader limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by “such as” and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for

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example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim 21 recites the limitation “salts advantageously being of the same nature.” It is unclear what is meant by “of the same nature.” The nature of the polysaccharide could refer to the structure of the polysaccharide, but the claim is drawn to a process comprising only hyaluronic acid salts; thus “of the same nature” must refer to other than hyaluronic acids. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuniak et al. (CA 949965, June 25, 1974, PTO-1449 submitted October 7, 2005).

Kuniak et al. teach the cross-linking of 100 parts of starch with 0.5 parts of epichlorohydrin in aqueous sodium hydroxide [page 15, Example 1]. The appropriate amount of crosslinking compound calculated on the weight of dry starch is 0.05-2.0% [claim 1]. Starch is a mixture of amylose (which has a low molecular weight) and amylopectin (which has a high molecular weight), and thus the claims are anticipated.

Claims 17-20, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Balazs et al. (US 4,582,865, PTO-1449 submitted October 7, 2005), or as being anticipated by Balazs et al. (US 4,582,865, PTO-1449 submitted October 7, 2005) in view of Desai et al. (J Pharm Sci 1995 Feb; 84(2): 212-5, abstract).

Balazs et al. teach the cross-linking of sodium hyaluronates having varying molecular weights using divinyl sulfone in aqueous sodium hydroxide [columns 5 and 6, Examples 1-5]. The ratio of HA/DVS was about 4.7 by weight [Example 1], or 0.2-2.0 by mole [Example 4]. The skilled artisan knows that hyaluronans have molecular weight dispersity, and thus a lower molecular weight HA was crosslinked with a higher molecular weight HA. HA was also cross-linked with carboxymethyl cellulose [column 7, Examples 10-13], with collagen [column 8, Examples 14 and 15], and with heparin [column 8, Example 16]. The skilled artisan knows that, in addition to molecular weight dispersity, HA does not have the same molecular weight as carboxymethyl cellulose, collagen, and heparin. For example, Desai et al. teach that heparin has a molecular weight of approximately 10,000 Da [abstract]. Thus, a low-molecular weight polysaccharide (heparin) was cross-linked with a high-molecular weight polysaccharide (HA).

Claims 17, 18, 19, 20, 26, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mälson et al. (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson et al. teach a gel of crosslinked hyaluronic acid [see abstract]. Sodium hyaluronate (400 mg) of molecular weight about 1×10^6 was dissolved in aqueous sodium hydroxide and cross-linked using 300 μL of 1,4-butanediol diglycidyl ether (BDDE) [column 5, Example 3]. Similar procedures were carried out using HA of molecular weight 3×10^6 [column 4, Example 1], 20,000 [column 5, Example 3], and 3×10^6 [column 5, Example 5]. The skilled artisan knows that hyaluronans have molecular weight dispersity, and thus a lower molecular weight HA was crosslinked with a higher molecular weight HA. The amounts of BDDE required to achieve gel formation are also taught [column 5, Table].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21-24 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Mälson et al. (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson et al. teach as set forth above.

Mälson et al. do not expressly teach the crosslinking of a hyaluronic acid salt of molecular weight of at most 9.9×10^5 and a hyaluronic acid salt of molecular weight of at least 10^6 Da. However, the skilled artisan knows that hyaluronans have molecular

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weight dispersity, and that the cross-linking of HA having a molecular weight about 1,000,000 is extremely likely to contain HA of molecular weight less than 990,000 and HA of molecular weight more than 1,000,000. It is also extremely likely that at least 5% of the HA was high-molecular weight hyaluronic acid (molecular weight more than 1,000,000). Claim 23 requires that the mixture contains more than 50% by weight of low molecular weight HA and less than 50% by weight of high molecular weight HA; because the average molecular weight of the HA taught by Mälson falls directly between Applicant's definition of low and high-molecular weight HA, it is extremely likely that about 50% falls under the "high" category and about 50% fall under the "low" category. The recitation of intrinsic viscosity in claim 22 is an intrinsic property of the composition and cannot be separated from it.

Claims 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mälson et al. (US 4,716,154, December 29, 1987, PTO-1449 submitted October 7, 2005).

Mälson et al. teach as set forth above. Mälson also teaches that HA has molecular weight varying within the range of 20,000 to 8,000,000 and that it is an easy matter to properly adapt the concentration, type of crosslinking agents employed and degree of crosslinking to the molecular weight of each particular starting material. If HA has a low molecular weight, greater concentration of HA and crosslinking agent will be needed as compared to HA which has a high molecular weight. A preferred range is from 500,000 to 3,000,000 [column 2, line 62 - column 3, line 17].

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Mälson et al. does not teach crosslinking of a mixture composed of 90% of HA having a molecular weight of about 3×10^5 Da and about 10% of HA having a molecular weight of about 3×10^6 Da. It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the conditions taught by Mälson et al. to arrive at the claimed invention. Mälson teaches the effect of molecular weight on reaction conditions, as set forth above. Mälson also provides guidance regarding the solids content of gel formation from HA of differing molecular weights [columns 4-6, Examples 1-10]. Thus, the skilled artisan could easily manipulate these in order to prepare a crosslinked HA gel having desired characteristics.

Further, the Supreme Court has determined, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. __, 82 USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not" be led only to those elements of prior art designed to solve the same problem " (KSR, 550 U.S. at __, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at __, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at __, 82 USPQ2d at 1397) and has further determined that "..... [t]he combination of familiar elements according to known methods is likely to

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be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that ". the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). In the instant case, the claimed invention is seen as the predictable use of prior art elements (crosslinking HA of different molecular weights) according to their established functions (gel formation). The claimed invention could also be seen as arranging old elements (crosslinking HA of different molecular weights) with each performing the same function it had been known to perform (gel formation), and thus is obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Tuesday - Friday, 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623